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Editorial Comment

Fate of Venous Grafts: The Past, The Present and the Future*

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The present study. In this issue of the Journal, FitzGibbon et al. (1) describe a long-term study in which consecutive postoperative angiographic examinations were performed on 741 saphenous vein grafts in 222 patients. All grafts were evaluated early (mean 0.96 months), at 1 year (mean 12.84 months) and >6.5 (mean 9.6) years after operation; the majority of these grafts (565) were also examined 5 years postoperatively. At the late examination, 237 grafts were restudied an average of 7.5 years, 403 an average of 10 years and 101 ≥11.5 years after operation. The subjects were mainly military personnel, all male, ranging in age from 31 to 67 years (mean 45.7).

Graft occlusion rates in these consecutive studies increased from 8% early, to 13% at 1 year and to 20% 5 years after operation. Late occlusion rates were 41% at 7.5 years, 41% at 10 years and 45% after 11.5 years. Early after operation no patent graft showed irregularities of outline; however, 7% showed a stenosis reducing the graft lumen to a diameter <50% of the grafted artery diameter. As shown in previous studies from our institution (2–4), most of these narrowings were at the distal anastomosis between the graft and the coronary artery and were presumably related to faulty surgical technique. At 1 year, 8% of patent grafts had at least some irregularities of outline. Six percent of them (that is, 0.5% of patent grafts) showed a narrowing that reduced the graft lumen by >50%. Although FitzGibbon et al. attribute this narrowing to graft atherosclerosis, we doubt that this was the case. Solymoss et al. (5) from our institution and other investigators (6) have not seen histologic evidence of graft atherosclerosis during the 1st 12 months after operation. In our experience these segmental narrowings are secondary to localized fibrointimal hyperplasia of vein grafts (2–4). By 5 years, 38% of patent grafts had irregularities of outline and were considered to have developed atherosclerosis. However, only 14% of them, that is, 5% of patent grafts, showed a >50% reduction of the graft lumen. Finally, at 10 years, 75% of patent grafts showed angiographic evidence of atherosclerosis. Thirty-five percent of them, (26% of all patent grafts) showed a >50% reduction of the graft lumen.

Clinical significance of study. Graft patency rates and the incidence of luminal irregularities or narrowings on the shaft of the graft or at the coronary anastomosis have been studied extensively at contrast angiography within the 1st 5 years after coronary artery bypass grafting (2,7–9). Overall, approximately 80% of saphenous vein grafts remain patent 5 years after operation. This includes a 5% to 10% incidence of graft closure within the 1st month, a 10% to 15% incidence at 1 year and a low incidence (5% to 10%) between 1 and 5 years after operation. Localized stenoses on the graft shaft or at the coronary anastomosis occur in 5% to 10% of cases early and relatively less often at 1 year. These narrowings, when they reduce the lumen of the graft by ≥50%, frequently lead to occlusion at subsequent examinations (2–4).

In contrast, few data are available on graft patency after 5 years, particularly on the rate and extent of progression of graft atherosclerosis between 5 and 10 years after operation and on the influence of these atherosclerotic changes on late graft occlusion (3,10–12). The present data by FitzGibbon et al. (1) support and confirm previous data from the Cleveland Clinic (12) and from our institution (3).

Previous studies. In 1983 Campeau et al. (3) from our institution reported sequential angiographic examinations at 2 weeks, 1 year, 5 to 7 years and 10 to 12 years after aortocoronary saphenous vein bypass grafting in 147 grafts from 82 unselected patients. Graft occlusion rates in these consecutive angiographic examinations were as follows: 3.4% at 2 to 3 weeks, 10% at 6 to 18 months, 19% at 5 to 7 years and 37% at 10 to 12 years after operation. Between 5 and 7 years, angiographic evidence of atherosclerosis was present in 16% of patent grafts. One third of these atherosclerotic grafts (5% of patent grafts) showed narrowings that reduced the graft lumen by ≥50%. In contrast, between 10 and 12 years after operation, 46% of patent grafts had angiographic evidence of atherosclerosis and 70% of them (32% of patent grafts) showed narrowings that reduced the graft lumen by ≥50%. Graft closure was 2.5 times more frequent during the 6 to 11 year interval as compared with the 1 to 6 year interval. Attrition was more prevalent in grafts with focal narrowings and with atherosclerosis at the previous examination.

Lytle et al. (12) from the Cleveland Clinic performed two successive postoperative angiograms in 501 patients and 786 saphenous vein grafts. All grafts were studied at ≤5 years (range 1 to 59 months, mean 15 months) and at >5 years (range 60 to 147 months, mean 88 months) after operation. An average of 7.3 years after operation, 36% of the grafts were occluded, 18% were stenotic (45% with graft lumen reduction of ≥50%) and 45% were widely patent.

Thus, despite obvious differences in study design and patient selection, the findings from these three groups are in relatively close agreement. Between 35% and 40% of vein grafts are occluded between 7 and 12 years (average 10) after

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coronary artery bypass grafting. As shown by our group and by FitzGibbon et al. (1), an additional 25% to 30% of these grafts show "significant" (≥50% luminal reduction) atherosclerotic narrowings. Overall, 60% to 70% of vein grafts can be considered to be functionally impaired an average of 10 years after operation.

The 7.5 year phenomenon. FitzGibbon et al. (1) observed that the greatest incidence of graft occlusion and of severe graft atherosclerosis occurred at 7.5 years after operation. This was followed by a more or less constant incidence of obstruction in grafts studied 10 and ≥11.5 years after operation. Graft occlusion increased from 20% at 5 years to 41% at 7.5 years. The number of grafts with ≥50% luminal narrowings increased from 5% at 5 years to 31% at 7.5 years. Our group (3) previously showed a marked acceleration of graft atherosclerosis and occlusion between 5 and 10 years after operation. FitzGibbon et al. (1) observed that primarily unscheduled symptomatic patients were restudied during this period. Indeed, this time interval corresponds to the period when severe symptoms often recur after coronary artery bypass grafting. It also coincides with a period of increased surgical mortality in the recent randomized trials of coronary bypass surgery (13–15).

Histologic studies (5) have shown a different aspect of the progression of graft atherosclerosis. Atherosclerosis was almost always absent in vein grafts examined during the 1st 12 months, and only 11% of grafts showed evidence of atherosclerosis between 1 and 3 years after operation. However, atherosclerosis was documented in 66% of grafts between 3 and 6 years and this incidence remained relatively constant between 6 and 13 years after operation.

Thus, the development of vein graft atherosclerosis reaches a peak between 3 and 6 years after operation. However, the disease usually does not progress to the symptomatic stage until several years later.

Diseased graft prognosis. FitzGibbon et al. (1) observed that diseased grafts became more diseased at subsequent examinations and that occlusion occurred in many. This phenomenon was well documented some years ago by our group (2,3) and by other investigators (12). For example, about half of the grafts with constricted anastomoses early after operation in our series were occluded at 1 year and half of the remaining grafts also occluded during the subsequent 10 years. Likewise, localized narrowings on the graft trunk at the 1 year examination often led to late graft occlusion, particularly when they reduced the graft lumen by ≥50%. Finally, the presence of atherosclerosis between 5 and 7 years after operation also strongly influenced late graft patency (3). Closure was noted between 10 and 12 years after operation in 43% of grafts with such lesions as compared with only 20% in unchanged grafts or in grafts with diffuse narrowing. However, the course of diffuse intimal fibromuscular hyperplasia noted between 6 and 18 months after operation constituted a notable exception in our patients. Even moderate to severe diffuse intimal hyperplasia showed no significant progression after the 1st year and this was not a determinant of late graft closure (3).

FitzGibbon et al. (1) also point out that absence of disease has little prognostic significance because diseased and occluded grafts were often generated by those with healthy appearances at earlier examinations. This is not at all surprising. Except for variable degrees of diffuse intimal hyperplasia, most patent grafts have a normal angiographic appearance 1 year after operation. Thus, grafts developing atherosclerosis at 5 years were usually considered healthy at 1 year and grafts showing late atherosclerotic changes or late occlusions were often considered healthy at 1 and 5 years after operation.

The future. In contrast to the saphenous vein, the internal thoracic artery remains free of atherosclerosis late after operation (10,16). Patency rates of almost 90% have been reported at 10 years. In recent years the internal thoracic artery has become the conduit of choice for coronary artery bypass grafting. However, as emphasized by FitzGibbon et al. (1), routine use of the right internal thoracic and right gastroepiploic arteries is often not practical and vein grafts are still needed in the majority of patients with multivessel disease. Therefore, we must actively pursue our quest for effective methods of improving their long-term patency.

Continued efforts to minimize endothelial and graft injury during saphenous vein harvesting by the use of meticulous surgical techniques is essential. Antiplatelet agents have been shown to effectively reduce early graft thrombosis in recent clinical trials (17,18). Their use should be mandatory during the 1st year after operation. The development and progression of atherosclerosis beyond the 1st year after operation may be related to the usual coronary risk factors and an adequate control of these factors is important. However, these measures have been adopted to a variable extent for a number of years and, as suggested by FitzGibbon et al. (1), they appear to have had a limited impact on long-term vein graft patency.

Future efforts should probably concentrate on three major areas: prevention of the development of atherosclerosis, prevention of the progression of atherosclerosis and prevention of late graft thrombosis.

Although this is still controversial, intimal fibromuscular hyperplasia may be a precursor of atherosclerosis in vein grafts. Because they do not adequately inhibit platelet adhesion to the exposed subendothelium, currently prescribed antiplatelet agents do not prevent the intimal hyperplasia of vein grafts. More potent platelet inhibitors, as well as inhibitors of smooth muscle cell proliferation, may be effective in preventing this lesion in the future. Some of these drugs are currently under investigation for the prevention of restenosis after coronary angioplasty.

Data from our institution (19) have shown that serum lipids may play a major role in the progression of atherosclerosis in vein grafts. A beneficial effect of a lipid-lowering regimen on progression and regression of atherosclerotic lesions was demonstrated recently (20,21) in both vein grafts

and native coronary arteries. Ongoing trials are attempting to confirm and extend these observations. Obviously, the long-term efficacy of these drug regimens will have to be documented.

Finally, late occlusion of vein grafts is almost regularly associated with thrombosis at the site of atherosclerotic lesions and, in that respect, the mechanism of late vein graft occlusion may be similar to that of coronary occlusion (5). The efficacy of antiplatelet agents and of oral anticoagulants in preventing late graft thrombosis has not been adequately documented. In addition, newer, more potent orally administered antithrombotic agents may become available in the future.

The long-term fate of aortocoronary saphenous vein bypass grafts provides a human model of rapid onset and progression of atherosclerosis and of late thrombosis. Effective measures modifying the atherosclerotic process in this model would undoubtedly be applicable to other vascular territories.

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